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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/653,406	09/01/2000	Jennifer L. West	RICE 100	7133

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Kilpatrick Stockton LLP
John S Pratt
1100 Peachtree Street N.E.
Suite 2800
Atlanta, GA 30309-4530

EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/653,406	WEST ET AL.	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,20-24 and 32-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18, 20-24 and 32-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of amendment and remarks filed 11/02/05. Claims 18, 20-24 and 32-46 are pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 18, 20-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The new method claims 32-44 flow from the generic claims and the issues raised herein applies to these dependent claims.

For rejections under 35 U.S.C. 112, first paragraph, the following factors must be considered (In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988)):

1) Nature of invention.

2) State of prior art.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure

4) Level of predictability in the art.

5) Amount of direction and guidance provided by the inventor.

6) Existence of working examples.

7) Breadth of claims.

8) Level of ordinary skill in the art.

See below:

In the instant case, applicants are claiming a method of treating a disorder or condition with nitric oxide in an individual administering a biocompatible polymerized macromer having one nitric oxide compound.

1) Nature of the invention.

The nature of the invention is methods of treating a disorder or condition with nitric oxide in an individual administering a biocompatible polymerized macromer having one nitric oxide compound. As stated, however, claim 20 recites that any or all-disorder or condition with nitric oxide is intended.

2) State of the prior art and the predictability or lack thereof in the art.

The state of the prior art Lin et al. ("Nitric Oxide-based molecular strategies for restenosis therapy" in Expert Opinion on Therapeutic Patents, 15:483-495 (2005)), discloses that "systemic NO donor administration for the clinical treatment of restenosis is impractical because of the large doses required to achieve an effective concentration at the vascular injury site, catabolism and elimination of the donor itself, and the likely distribution of active NO donor to peripheral tissues outside of the target vessel." Clinical treatment of restenosis involves screening *in vitro* and *in vivo* to determine which compounds exhibited the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18

(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

Thus, in the absence of a showing of correlation between all the diseases claimed as capable of being treated by compounds of the instant claims, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compounds due to the unpredictability of the role of NO donor and diseases treatable by the NO donor.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed requires undue experimentation. One of ordinary skill in the art would first need to determine all the disorder or conditions effectively treatable by the NO donor, and then determine which of the many NO donors would be suitable for said treatment.

4) Level of predictability in the art.

The art pertaining to the treatment of disorder or conditions by administering NO donor remain highly unpredictable. As disclosed above, there is no absolute predictability even in view of the seemingly high level of skill in the art. Firstly, for a compound or genus to be effective against any disorder or condition as claimed is generally is contrary to medical science. The vast number of disorder or condition that may be treatable with NO is a condition or disoder that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the conditions or disorder that is mdiated by NO. There is no common mechanism by which all or even most disorders or conditions arise in the biological system. Accordingly, treatments for disorders of conditions associated with NO must be tailored to the type of condition, as there is no, and there can be no "magic bullet" against disoders and conditions of the biological system.

5) Amount of direction and guidance provided by the inventor.

The amount of direction or guidance present is found in the examples wherein NO donor molecules are synthesized and tested for *in vitro* release of the NO using cultured smooth muscle cells and on platelet adhesion. However, the direction provided by the examples is limited to *in vitro* analysis using two systems and to the conditions of cell proliferation and platelet adhesion. These conditions are very limited to the broad genus of disorders and conditions, which can be anything or any disorder and any condition. Thus the one would have to experiment with a lot more disorders and NO donors to arrive at what works and what does not. In addition, the gap between *in vitro* activity and *in vivo* utility is large enough to warrant thorough and compelling *in vivo* or clinical data.

6) Existence of working examples.

As discussed above, working example is found in the Examples wherein *in vitro* analysis is conducted on two systems. Applicants' limited working example does not enable one of ordinary skill in the art to treat the varied and numerous disorders and conditions encompassed by the claimed invention.

7) Breadth of claims.

Claims 18 and 20 are extremely broad due to the vast number of possible disorders and conditions and NO modulating compound.

8) Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Hence, the specification fails to provide sufficient support of the broad use of NO donors or NO modulating compounds for the treatment of any disorder or condition of the biological system. One of ordinary skill in the art is thus necessitating, as a result, to perform an exhaustive search to determine which disorders and conditions can be treated by what NO donors of the instant claims in order to practice the claimed invention.

Genentec Inc. V. *Novo Nordisk A/S* (CAFC) 42 USPQ 2D 1001, states:

"a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds encompassed in instant claims, with no assurance of success.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms, and treatment (or lack thereof) for all disoders, conditions and restenosis. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

This rejection can be overcome by reciting specific closely related diseases.

The rejection of claim 23 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating surgical adhesions, does not reasonably provide enablement for preventing surgical adhesions is withdrawn in view of the amendment.

Regarding claims 22 and 24, the prior art, Lin is clear of the difficulty of systemic administration of No donor to effectively treat restenosis. Wound encompasses a variety of conditions and there is no specific disclosure for the types of wound that can be treated with NO donor or the type of NO donor that can be employed to treat the **wound**. There is no relationship of the conditions listed in claim 22 and because the NO nor treatment art is

unpredictable (see Lin); the guidance given is not adequate to guide the ordinary or the skilled artisan. The relationship of restenosis and erectile dysfunction is not made; the relationship of thrombosis and asthma and erectile dysfunction is not also not made. This is only a representative sample of what is not clear about the relatedness of all the conditions listed in the claims. The conditions appear not related. The other question remains: how possible/probable is it for the NO carrying macromer to be effective in treating all these unrelated conditions? There is no clear association that NO will treat all and every condition and disorder. The doses have not been worked out for the various disorders and conditions

3. The rejection of claims 22 and 24 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which applicant regards as the invention is withdrawn in view of the amendment.

4. The rejection of claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

5. NEW MATTER

6. Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The recitation of "affected by NO" has no support in the specification as originally filed.

Double Patenting

7. Claims 20-24 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-25 of copending Application No. 10/129418. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn method of treatment comprising administering macromer composition comprising nitric oxide (NO).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants state that a Terminal disclaimer would not be filed in this application because one has been filed in the co-pending application that has been allowed.

8. Applicants' arguments filed 11/02/05 have been fully considered but they are not persuasive. Terminal disclaimers do not carry over from one application/patent to the other. The filling date is not exclusionary to the filing of a terminal disclaimer. .

The instant claims are directed to method for controlled release of therapeutic or diagnostic agents and the method comprises administering to a tissue in need thereof, a biocompatible, polymerizable macromer composition that comprises at least one nitric oxide (NO) carrying region...and wherein the NO or the NO modulating compound is released from the macromer composition following in situ polymerization.... Based on the method where the composition polymerizes in situ to release the NO or the NO modulating compound, the following art of interest is noted.

Smith et al. (WO 96/32136, cited on PTO Form 1449) discloses that a polymer bound nitric oxide/nucleophile adduct composition can be applied with specificity to a biological site of

interest and the site specific application of the polymer bound adduct composition enhances the selectivity of the action of the nitric oxide releasing $N_2O_2^-$ functional group (page 7, lines 19-35). The nitric oxide is bound to the polymer physically or chemically (page 6, lines 22-30). The composition of Smith is not a prepolymer that would polymerize in situ to release NO under physiological conditions.

Diodati et al. ("Complexes of Nitric Oxide with Nucleophiles as Agents for the Controlled Biological Release of Nitric Oxide: Hemodynamic Effect in the Rabbit," in Journal of Cardiovascular Pharmacology, 22:287-292, cited on PTO Form 1449) discloses the hymodynamic effect of Nitric Oxide/Nucleophile complexes. These complexes do not polymerize in situ to release NO.

Saavedra et al. (US 5,632,981) discloses nitric oxide/nucleophille complexes that are capable of releasing nitric oxide under physiological conditions and the complex comprises peptide, polypeptide, protein or nucleic acid, to which is bound nitric acid releasing compound (abstract; column 3, lines 55-60; column 5, lines 55-60; column 6, lines 45-49). The complex of Saavedra does not polymerize in situ to release nitric oxide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 3:30 p.m. (Monday to Friday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Blessing Fubara
Patent Examiner
Tech. Center 1600